CHRONIC TOXICOLOGY SUMMARY

ETHYLENE GLYCOL

(1,2-dihydroxyethane; 1,2-ethanediol)

CAS Registry Number: 107-21-1

I. Chronic Toxicity Summary

Chronic reference exposure level	**400** µg/m^3 (200 ppb)
Critical effects	Respiratory irritation in human volunteers
Hazard index target(s)	Respiratory system; kidney; teratogenicity

II. Physical and Chemical Properties (HSDB, 1996; 1999)

Description	Clear, colorless, odorless liquid
Molecular formula	$C_2H_6O_2$
Molecular weight	62.07 g/mol
Density	1.1088-1.1135 g/cm^3 @ 20° C
Boiling point	197.6° C
Melting point	–13° C (CRC, 1994)
Vapor pressure	0.06 torr @ 20°C; 0.092 torr @ 25°C
Solubility	Soluble in water and ethanol; slightly soluble in ether. Insoluble in benzene and petroleum ether.
Conversion factor	1 ppm = 2.5 mg/m^3 @ 25° C

III. Major Uses and Sources

Ethylene glycol is used as an antifreeze agent in cooling and heating systems (HSDB, 1996). It is used in hydraulic brake systems; as an ingredient in electrolytic condensers; as a solvent in the paint and plastics industries; and in inks for ball-point pens and printer's inks. It is used in the manufacture of some synthetic fibers (Terylene and Dacron), and in synthetic waxes. It is used in some skin lotions and flavoring essences. Also, it is used in asphalt emulsion plants, in wood stains and adhesives, and in leather dyeing. It has been used as a de-icing fluid for airport runways. The annual statewide emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 66,636 pounds of ethylene glycol (CARB, 1999).

IV. Effects of Human Exposure

Laitinen *et al.* (1995) found that 10 motor servicing workers had significantly higher urinary levels of ethylene glycol and ammonia, and decreased urinary glycosaminoglycan levels, compared with 10 controls. The ethylene glycol levels in air were undetectable in the workers' breathing zones (i.e. below 1.9 ppm), therefore dermal absorption appeared to be the primary route of exposure. Because the dermal absorption rate is high, airborne ethylene glycol concentrations in workplaces likely underestimate the total exposure.

In a study of 20 volunteer male prisoners in Alabama, 20 hour/day exposure to aerosolized ethylene glycol concentrations varying up to a mean of 20 ppm (49 mg/m^3) for 30 days was without effect (Wills *et al.*, 1974). The actual concentrations measured in the exposure chamber were:

Concentration of ethylene glycol in air (mg/m^3)

Days	Low	High[a]	Mean
1-7	3.6	75.0	37
8-14	18.8	44.8	29
15-21	0.8	41.6	17
22-28	3.5	49.2	23
29-35	20.6	66.8	49
36-37	14.4	39.0	31

[a] does not include the very high concentrations maintained for comparatively brief periods.

Respiratory irritation was noted after 15 minutes at an exposure concentration of 75 ppm (188 mg/m^3), and became quickly intolerable at 123 ppm (308 mg/m^3). No effects were observed in normal clinical chemistry, clinical serum enzyme levels for liver and kidney toxicity (including SGOT and serum alkaline phosphatase), hematotoxicity (including % hematocrit and gm hemogloin per 100 ml blood), or psychological responses (including simple reaction time, weight discrimination, and depth perception). The respiratory irritation at 75 ppm resolved soon after exposure with no long term effects noted after a 6-week follow-up period.

V. Effects of Animal Exposure

A chronic feeding study in rats and mice was conducted by DePass *et al.* (1986a). In this study, rats (130 per sex per group) and mice (80 per sex per group) were exposed to 0, 0.04, 0.2, or 1 g/kg/day for up to 2 years. All male rats in the high dose group died by 475 days. A large number of effects were observed in this group, including: reduced body weight, increased water intake, increased blood urea nitrogen and creatinine, reduced erythrocyte counts, reduced hematocrit and hemoglobin, increased neutrophil count, and increased urine volume. Heart, kidney, lung, parathyroid, stomach, and other vascular mineralization and hyperplasia were observed histologically in the high dose group of the male rats. Female rats exhibited fatty changes and granulomas in the liver at the high dose. Liver effects were not reported for the males. The NOAEL in rats for chronic oral ethylene glycol toxicity was 200 mg/kg/day. No effects were observed in mice. Therefore, the NOAEL for mice was 40 mg/kg/day.

Coon *et al*. (1970) exposed groups of rats (as well as guinea pigs, rabbits, dogs, and monkeys) to ethylene glycol intermittently 8 hours/day, 5 days per week for 6 weeks (30 exposures) to 10 or 57 mg/m^3 or continuously to 12 mg/m^3 for 90 days. At 10 mg/m^3 2 rabbits had conjunctivitis and liver changes were noted in a few animals of the other species. At 57 mg/m^3 no signs of toxicity were seen during the exposure. Nonspecific inflammatory changes were noted in some lungs and hearts of all species. A few livers also showed necrotic areas. Continuous exposure to 12 mg/m^3 led to moderate to severe eye irritation in rats and rabbits. Edema in the rabbits led to eye closure. Two rats developed corneal opacities. All hematologic parameters and various enzymes assayed were within normal limits. At necropsy organs appeared normal. Histopathological analysis revealed inflammatory changes in the lungs of all species, but

the controls also showed a lesser degree of inflammation. Several guinea pigs showed foci of inflammatory cells in the kidney.

Mortality in Coon *et al.* (1970)

<----------Number died/number exposed----------->

Ethylene glycol (mg/m^3)	Exposure duration	Equivalent continuous concentration	Rat	Guinea pig	Rabbit	Dog	Monkey
0 (control)	90 days	0	4/123	0/73	0/12	0/12	0/8
10±1	6 wk	2.4	0/15	0/15	0/3	0/2	0/2
57±14	6 wk	13.6	0/15	0/15	0/3	0/2	0/2
12±2	90 days	12.0	1/15	3/15	1/3	0/2	0/3

Studies on the effects of inhaled ethylene glycol on reproduction and development of rats and mice were conducted by Tyl *et al.* (1995a, 1995b). In a study using whole-body exposure of rats and mice to ethylene glycol at analyzed concentrations of 0, 119, 888, or 2090 mg/m^3 for 6 hours/day on days 6-15 of gestation, mice were found to be the more sensitive species. Maternal toxicity in rats included a significant increase in absolute and relative liver weight at 2090 mg/m^3. No effects on weight gain, organ weights other than liver, fecundity, live fetuses per litter, or pre- or post-implantation loss were observed in rats. In addition, terata were not observed at any concentration. Reduced ossification in the humerus, zygomatic arch, and the metatarsals and proximal phalanges of the hindlimb was present in fetuses exposed to 888 or 2090 mg/m^3. The NOAEL for maternal toxicity in rats was 888 mg/m^3, while the NOAEL for fetotoxicity was 119 mg/m^3.

In mice, reduced body weight and gravid uterine weight during and after the exposure were observed at the 888 and 2090 mg/m^3 concentrations. Increased nonviable implants per litter and reduced fetal body weights were also observed in groups exposed to 888 or 2090 mg/m^3. External, visceral, skeletal, and total malformations were increased in the 888 and 2090 mg/m^3 groups. The NOAEL for these effects in mice was 119 mg/m^3.

A similar experiment in mice using nose-only exposures was conducted by these researchers (Tyl *et al.*, 1995a) to determine the role of dermal absorption and/or ingestion on the effects observed with the whole-body exposure. Nose-only exposures to ethylene glycol were for 6 hours/day, on gestational days 6 through 15 at concentrations of 0, 500, 1000, and 2000 mg/m^3. The NOAEL for maternal effects (increased kidney weight) was 500 mg/m^3, and the NOAEL for fetal toxicity (skeletal variations and fused ribs) was 1000 mg/m^3. Thus, secondary dermal and/or oral exposures appear to have contributed significantly to the developmental and maternal toxicity in mice exposed to ethylene glycol aerosol. The nose-only inhalation exposure study by Tyl *et al.* (1995a) was conducted in addition to the whole-body inhalation study since extensive adsorption of ethylene glycol onto the fur of the animals was demonstrated in the whole-body experiment. Normal grooming behavior would have resulted in significantly larger doses of ethylene glycol than that expected by inhalation only.

A 3-generation study on the effects of ethylene glycol on reproductive performance and gross health of offspring in rats was conducted by DePass *et al.* (1986b). Rats were exposed orally to 40, 200, or 1000 mg/kg/day ad libitum in the feed through 3 generations. No effects on pup survivability or pup body weight were observed. Total and viable implants were also not affected. Teratogenic effects were not examined in this study.

Tyl *et al.* (1993) studied the reproductive and developmental effects of ethylene glycol in rabbits exposed by gavage on days 6 to 19 of gestation. Dams were exposed to 0, 100, 500, 1000, or 2000 mg/kg/day. Exposure to 2000 mg/kg/day resulted in 42% mortality, and abortion or early delivery in 4 does. No evidence of embryotoxicity or teratogenicity was observed in the groups exposed to 1000 mg/kg/day or less. The NOAEL for maternal toxicity was determined to be 1000 mg/kg/day.

VI. Derivation of Chronic Reference Exposure Level

Study	Wills *et al.* (1974)
Study population	Human volunteer prisoners
Exposure method	Discontinuous whole-body inhalation
Critical effects	Respiratory tract irritation
LOAEL	75 ppm
NOAEL	20 ppm
Exposure continuity	20 hours/day
Exposure duration	30 days
Average exposure	16.7 ppm for NOAEL group (20 x 20/24)
Human equivalent concentration	16.7 ppm
LOAEL uncertainty factor	1
Subchronic uncertainty factor	10
Interspecies factor	1
Intraspecies factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.2 ppm (200 ppb; 0.4 mg/m^3; 400 $\mu g/m^3$)

The subchronic study by Wills *et al.* (1974) represents the only human inhalation data for ethylene glycol toxicity. The experiment showed a concentration-response relationship, with onset of irritation occurring at 188 mg/m^3 and intense and intolerable irritation occurring at 308 mg/m^3. The volunteers were followed for 6 weeks without any apparent long-term effects from the exposures. Although the irritation experienced in the human subjects appears to be an acute phenomenon and not a cumulative lasting effect, the subchronic uncertainty factor of 10 was retained to protect against other systemic effects associated with ethylene glycol such as kidney damage which may occur over a long-term exposure.

The chronic feeding study in rats by DePass *et al.* (1986a) showed significant chronic effects. These included reduced body weight, increased water intake, increased blood urea nitrogen and creatinine, reduced erythrocyte counts, reduced hematocrit and hemoglobin, increased neutrophil counts, increased urine volume, and reduced urine specific gravity and pH in rats exposed to a concentration of 1000 mg/kg/day. However, no effects were reported in mice. In contrast, reproductive and developmental toxicity studies in mice, rats, and rabbits have shown the mouse to be the most sensitive species for both terata and maternal toxicity endpoints (Tyl *et al.*, 1995a; Tyl *et al.*, 1993; Neeper-Bradley *et al.*, 1995). In addition, the 3-generation reproductive toxicity study by DePass *et al.* (1986b) showed no significant effects on rat pup survival or body weight at concentrations up to 1000 mg/kg/day. However, developmental endpoints were not reported in this study. From the available data, the toxicity of ethylene glycol is apparently greatest in the maternal mouse. The estimated equivalent air concentrations (assuming a 70 kg human inhales 20 m^3/day) from the feed in the 3-generation study by DePass *et al.* (1986b) are 700 mg/m^3 and 3500 mg/m^3 for the NOAEL and LOAEL, respectively.

For comparison with the proposed REL of 400 $\mu g/m^3$ based on a one month human study, the inhalation NOAEL of 48 ppm, obtained by Tyl *et al.* (1995) in mice discontinuously exposed for 10 days on gestation days 6-15, was used to estimate a REL based on animal data. Use of a time adjustment from 6 to 24 hours/day, an RGDR of 1, an interspecies UF of 3, and an intraspecies UF of 10 resulted in an estimated REL of 0.4 ppm (1000 $\mu g/m^3$) for ethylene glycol.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for ethylene glycol include the use of human exposure data, the use of controlled, nearly continuous inhalation exposures, the observation of a NOAEL, and the similar REL value estimated from an animal study. Major areas of uncertainty are the short length of the key study and the lack of chronic inhalation exposure studies in both animals and man (LaKind *et al.*, 1999).

VIII. References

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